



Sickle Cell Disease Agents Therapeutic Class Review (TCR)

March 8, 2021

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

| Drug | Manufacturer | Indication(s) |
|---|---------------------------|---|
| crizanlizumab-tmca (Adakveo®) ¹ | Novartis | To reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients ages ≥ 16 years with sickle cell disease (SCD) |
| hydroxyurea (Droxia®) ² | Bristol-Myers Squibb | To reduce the frequency of painful crises and to reduce the need for blood transfusions in adult patients with sickle cell anemia with recurrent moderate to severe painful crises |
| hydroxyurea (Siklos®) ³ | Medunik USA | To reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients ages ≥ 2 years with sickle cell anemia with recurrent moderate to severe painful crises |
| L-glutamine (Endari®) ⁴ | Emmaus | To reduce the acute complications of SCD in adult and pediatric patients ages ≥ 5 years |
| voxelotor* (Oxbryta®) ⁵ | Global Blood Therapeutics | Treatment of SCD in adults and pediatric patients ages ≥ 12 years |

* Voxelotor (Oxbryta) was approved by the United States (US) Food and Drug Administration (FDA) as an Accelerated Approval based on voxelotor's ability to increase hemoglobin (Hb) levels. Continued approval of voxelotor may be contingent upon additional results from confirmatory trial(s).

OVERVIEW

Sickle cell disease (SCD) is an inherited red blood cell (RBC) disorder caused by a single gene mutation in the β -globin gene resulting in abnormal hemoglobin (Hb).^{6,7} It affects approximately 100,000 patients in the US and is more common among African Americans, although it is also seen in people of Hispanic ancestry. About 1 in 365 African Americans are born with SCD, and 1 in 13 have sickle cell trait (carrier). In Hispanic Americans, SCD occurs in 1 in 16,300 births. People with SCD have a reduced life expectancy by approximately 30 years.

People with SCD inherit 2 abnormal Hb genes, 1 from each parent.^{8,9} Sickle cell disease (SCD) comprises several syndromes in which the sickle mutation is inherited along with a mutation at the other beta globin allele that diminishes or eliminates the normal production of beta globin. These include sickle cell anemia (homozygous sickle mutation; HbSS), sickle beta thalassemia (HbS β), and hemoglobin SC disease (HbSC), among others. There are 2 types of beta thalassemia: "0" and "+". HbS β 0 thalassemia is usually a severe form of SCD, while HbS β 0+ thalassemia tends to be a milder form. Sickle cell anemia is the most common and most severe form of SCD. Sickle cell trait (SCT) is diagnosed when one normal gene and one abnormal gene are inherited. Patients with SCT do not have signs or symptoms of SCD, but they can pass the abnormal gene to their children.

In SCD, RBCs become crescent or "sickle"-shaped, sticky, and inflexible.¹⁰ The abnormal RBCs are also fragile, with a shortened cell life (a decrease to about 10 to 20 days instead of 90 to 120 days). Onset of signs and symptoms of SCD typically occurs at 5 to 6 months of age. Early symptoms include jaundice, fatigue, and swelling and pain of the hands and feet.^{11,12} While anemia associated with SCD is usually mild to moderate, severe anemia can occur, which can be life-threatening. The hallmark of SCD is painful vaso-occlusive crisis (VOCs) that arises when the abnormally shaped RBCs adhere to blood vessel walls, resulting in blockage of small blood vessels, reduced oxygen flow to tissues, and organ damage, including damage to the spleen, brain, eyes, lungs, liver, heart, kidneys, joints, bone, penis, and skin. While most

children with SCD are pain-free between crises, adolescents and adults may suffer with chronic pain. VOCs can have sudden onset, last hours to days, and can lead to chronic disability or death. Triggers include hypoxemia, dehydration, and change in body temperature. Chronic pain and anemia associated with SCD can interfere with activities of daily living (ADLs) and quality of life (QOL).

Treatment goals in patients with SCD focus on management of symptoms and disease complications.¹³ Strategies include management/prevention of disease sequelae, including VOC, chronic pain (managed with opioid and non-opioid analgesics), chronic hemolytic anemia, organ damage, pulmonary hypertension, and infection. A hematopoietic cell transplant (HCT) is the only cure for SCD, but its use is limited by associated risks and lack of matched donors. HCT is typically performed in children with complications such as strokes. For treatment of acute VOCs, intravenous (IV) hydration and analgesia are the mainstay of therapy. Blood transfusions are often used to treat and prevent complications of SCD, particularly in patients at risk for stroke. However, regular administration of transfusions are associated with iron overload and alloimmunization. Individuals with SCD are also at increased risk for bacterial and viral infections; therefore, immunization and prophylactic penicillin are important aspects of care during early childhood (ages < 5 years).

For decades, oral hydroxyurea (Droxia, Siklos) was the only approved pharmacologic treatment for SCD in the US.^{14,15} Hydroxyurea reduces the frequency of vaso-occlusive events and is indicated to reduce the need for blood transfusion in patients with recurrent VOCs. In 2017, the US Food and Drug Administration (FDA) approved the oral amino acid L-glutamine (Endari) to reduce acute complications of SCD. This was followed by approval in late 2019 of oral voxelotor (Oxbryta), for the treatment of SCD, and the IV monoclonal antibody crizanlizumab-tmca (Adakveo), to reduce the frequency of VOCs in adults and pediatric patients with SCD.

Stroke, silent cerebral infarcts (silent strokes), and cognitive impairment are common permanent sequelae of SCD.¹⁶ The American Society of Hematology (ASH) 2020 guidelines for the management of sickle cell disease and primary stroke prevention suggest considering hydroxyurea treatment at the maximum tolerated dose to substitute for regular blood transfusions in children (ages 2 to 16 years) with abnormal transcranial doppler ultrasound (TCD) results who have been receiving transfusion therapy for at least 1 year and want to stop transfusion (conditional recommendation, low certainty of evidence). ASH also suggests hydroxyurea treatment with at least 20 mg/kg per day at a fixed-dose or the maximum tolerated dose for children (ages 2 to 16 years) with HbSS, HbS β^0 thalassemia, or compound heterozygous SCD who have abnormal TCD screening and live in low-middle-income settings (where regular blood transfusion therapy and chelation therapy are not available or affordable) (conditional recommendation based, low certainty of evidence). For secondary stroke prevention, ASH recommends a blood transfusion goal of increasing the hemoglobin > 9 g/dL at all times and maintaining the HbS level at < 30% of total hemoglobin until the time of next transfusion for children with HbSS or HbS β^0 thalassemia and a history of prior ischemic stroke. In addition, ASH acknowledges that for secondary stroke prevention in children who cannot be transfused or refuse transfusion, hydroxyurea therapy is an inferior alternative to regular blood transfusions but is a superior option to no therapy at all.

The ASH 2019 guidelines for cardiopulmonary and kidney disease associated with sickle cell disease state that it is important to consider initiation and/or optimization of disease-modifying therapy, such as hydroxyurea or chronic transfusion, for the treatment of patients with pulmonary arterial hypertension (PAH) with confirmed right-heart catheterization (conditional recommendation, low certainty of evidence).¹⁷ For children and adults with SCD and worsening anemia associated with chronic kidney

disease (CKD), ASH also suggests combination therapy with hydroxyurea and erythropoiesis-stimulating agents (ESA) (conditional recommendation, very low certainty of evidence). In addition, ASH remarks that for patients at steady-state on hydroxyurea, ESAs are appropriate in the setting of CKD when there is a simultaneous drop in hemoglobin and absolute reticulocyte count. While on ESAs, optimizing adherence to hydroxyurea therapy may help maximize fetal hemoglobin responses for patients treated with combination therapy.

The American Thoracic Society 2014 guidelines regarding PAH in patients with SCD strongly recommends hydroxyurea as first-line therapy in patients with increased mortality risks; chronic transfusions are considered an alternative therapy (weak recommendation).¹⁸

The ASH 2020 guidelines for sickle cell disease and management of acute and chronic pain suggests against chronic monthly transfusion therapy as a first-line strategy and to prevent or reduce recurrent acute pain episodes (conditional recommendation, low certainty of evidence).¹⁹ Additionally, in unique circumstances when all other measures have failed to control recurrent pain episodes, including use of hydroxyurea and other disease modifying therapies, a trial of monthly transfusions may be reasonable. The panel suggests exercising caution if considering cessation of chronic transfusion therapy and initiation of other disease-modifying therapies and increase surveillance. The panel chooses not to offer a recommendation for or against chronic monthly transfusion therapy for pain management. The ASH acknowledges that L-glutamine and crizanlizumab reduce the rate of acute pain episodes in children and adults treated in acute care settings (e.g., infusion centers/day hospitals, and hospitals), but the panel does not offer specific guidance on their use.

The National Heart, Lung, and Blood Institute's (NHLBI) 2014 guidelines for the management of sickle cell disease recommend hydroxyurea in adults who have had ≥ 3 SCD-associated moderate to severe pain crises in a 12-month period (strong recommendations, high-quality evidence).²⁰ Hydroxyurea is also recommended in adults with SCD-related pain or severe chronic anemia (strong, moderate [for both]), as well as those with a history of severe and/or recurrent acute coronary syndrome or severe symptomatic chronic anemia (strong, moderate). The panel advises that hydroxyurea should be offered to pediatric patients ages ≥ 9 months regardless of clinical severity to reduce SCD-related complications (strong, high-quality for ages 9 to 42 months; moderate, moderate-quality for ages > 42 months). The addition of hydroxyurea to erythropoietin in adults and children with CKD can improve anemia (weak, low). An expert in SCD management should be consulted regarding hydroxyurea therapy for patients with HbS β^+ thalassemia or HbSC who experience recurrent SCD-related pain that interferes with ADLs or QOL (moderate, low) and those who are experiencing a clinical response to appropriately prescribed hydroxyurea (moderate, very low). The NHLBI advises that long-term treatment with hydroxyurea is indicated in patients with clinical response. Hydroxyurea is also recommended in children and adults who have had a stroke when implementation of a transfusion program is not possible (moderate, low-quality). L-glutamine (Endari), crizanlizumab-tmca (Adakveo), and voxelotor (Oxbryta) were not FDA-approved at the time these guidelines were developed.

PHARMACOLOGY^{21,22,23,24,25}

Adhesion molecules, such as P-selectin are expressed on platelets and endothelial cells and play an important role in VOC manifestation. Crizanlizumab-tmca (Adakveo) is a humanized IgG2 kappa monoclonal antibody that binds to P-selectin and blocks interactions with its ligands including P-selectin glycoprotein ligand 1. Binding P-selectin on the surface of the activated endothelium and platelets

inhibits interactions between endothelial cells, platelets, red blood cells, and leukocytes. Crizanlizumab-tmca inhibits adhesion of sickled RBCs, platelets, and leukocytes to blood vessel walls, thereby preventing VOC occurrence.

Hydroxyurea (Droxia, Siklos) is an antimetabolite that may inhibit DNA synthesis by acting as a ribonucleotide reductase inhibitor, without affecting the synthesis of ribonucleic acid or of protein. Hydroxyurea may increase hemoglobin F (HbF) levels in RBCs, decrease neutrophils, increase the water content of RBCs, increase deformability of sickled cells, and alter the adhesion of RBCs to endothelium. However, the association between hydroxyurea concentrations, reduction of crisis rate, and increase in HbF is unknown.

The pyridine nucleotides, NAD⁺ and its reduced form NADH, are involved in regulating and preventing oxidative damage in RBCs, which are more susceptible to oxidative damage than normal RBCs. L-glutamine (Endari), an amino acid supplement, increases the availability of reduced glutathione and may improve the NAD redox potential in sickle RBCs.

Voxelotor (Oxbryta) is a hemoglobin S (HbS) polymerization inhibitor. It binds to HbS and increases the affinity of HbS for oxygen. It may also affect RBC by reducing RBC sickling and deformability.

PHARMACOKINETICS^{26,27,28,29,30}

| Drug | Tmax | Half-life | Metabolism | Elimination |
|---------------------------------|-----------|------------|--|---|
| crizanlizumab-tmca (Adakveo) | nr | 7.6 days | Catabolic pathways | nr |
| hydroxyurea (Droxia, Siklos) | 1-4 hours | nr | Saturable hepatic metabolism (primary) and degradation by intestinal bacteria urease | Urine: 40% |
| L-glutamine (Endari) | nr | 1 hour | Not specified | Eliminated by glomerular filtration, but is completely reabsorbed |
| voxelotor (Oxbryta) | 2 hours | 35.5 hours | Oxidation (primarily CYP3A4) and reduction, and glucuronidation | Feces: 62.6% Urine 35.5% |

Tmax = time to maximum serum concentration; nr = not reported

A high-fat, high-calorie meal increased voxelotor exposure (area under the concentration curve [AUC]) by 42% and maximum concentration by 45% in whole blood compared to when taken during a fasted state.

CONTRAINDICATIONS/WARNINGS^{31,32,33,34,35}

There are no contraindications associated with crizanlizumab-tmca (Adakveo) or L-glutamine (Endari).

Hydroxyurea (Droxia, Siklos) and voxelotor are contraindicated in patients with known hypersensitivity to any component of the product. Hypersensitivity to voxelotor may present as rash, urticaria, mild shortness of breath, mild facial swelling, and/or eosinophilia.

Hydroxyurea carries a boxed warning for risk of severe myelosuppression, which can be life-threatening. Treatment should not be started in patients with significant bone marrow suppression (e.g., leukopenia).

Blood counts should be monitored at baseline and every 2 weeks during therapy. Dosage interruption or reduction may be required; therapy may be restarted after hematologic recovery, usually approximately 15 days after interruption. Pediatric patients are at a higher risk for myelosuppression during dose adjustments.

The boxed warning also informs that hydroxyurea is a human carcinogen. Secondary leukemia has been reported with long-term use. Patients treated with hydroxyurea should use sun protection. In addition, hydroxyurea is a cytotoxic drug; therefore, patients should be advised of its special handling and disposal procedure.

Based on the drug's mechanism of action and results of animal studies, hydroxyurea is expected to cause embryofetal harm if taken during pregnancy. Female patients of reproductive potential and male patients with female sexual partners of reproductive potential should use effective contraception during treatment and for 6 or 12 months after discontinuation of treatment with hydroxyurea tablets (Siklos) and hydroxyurea capsules (Droxia), respectively.

Hydroxyurea may cause cutaneous vasculitic toxicities, such as ulcerations and gangrene, and its use should be avoided in patients with leg ulcers.

Pancreatitis, hepatotoxicity, and peripheral neuropathy have been reported with concurrent use of hydroxyurea and antiretroviral (ARV) drugs (e.g., didanosine, stavudine).

Administration of live virus vaccines should be avoided in patients treated with hydroxyurea.

Macrocytosis may occur early in treatment with hydroxyurea and may mask a diagnosis of pernicious anemia; therefore, concurrent use of folic acid is recommended.

Hydroxyurea may lead to falsely elevated laboratory values for uric acid, urea, or lactic acid.

The labeling for hydroxyurea capsules (Droxia) also warns that the product has been associated with interstitial lung disease, including pulmonary fibrosis, lung infiltration, pneumonitis, and alveolitis in patients treated for myeloproliferative neoplasm (not a FDA-labeled use). Patients should be monitored for respiratory symptoms (e.g., cough, pyrexia, dyspnea) and, if these occur, hydroxyurea should be discontinued promptly and the patients should be managed with corticosteroids.

Patients should be monitored for signs and symptoms of infusion-related reactions, such as fever, chills, nausea, vomiting, fatigue, dizziness, pruritus, urticaria, sweating, shortness of breath, or wheezing. Discontinue crizanlizumab-tmca infusion and initiate appropriate medical care if a severe reaction occurs. Automated platelet count interference (platelet clumping) was reported following crizanlizumab-tmca administration, particularly when blood collection tubes contained ethylenediaminetetraacetic acid (EDTA). This may lead to unevaluable or a falsely reported decrease in platelet count. Blood samples should be run within 4 hours of collection, or the blood should be collected in tubes containing citrate.

Voxelotor (Oxbryta) may alter or interfere with measuring Hb or its subtypes (HbA, HbS, and HbF). If exact measurement is required, the laboratory analysis should be performed when the patient is not taking voxelotor.

DRUG INTERACTIONS^{36,37,38,39,40}

Crizanlizumab-tmca (Adakveo) administration has led to interference with automated platelet counts due to platelet clumping when blood samples were collected in tubes containing EDTA.

Pancreatitis, including fatal cases, and peripheral neuropathy, including severe cases, have been reported in patients with human immunodeficiency virus (HIV) infection who were treated with concurrent hydroxyurea and didanosine, with or without stavudine. Hydroxyurea should be permanently discontinued if pancreatitis is suspected.

Postmarketing cases of hepatotoxicity, including hepatic failure resulting in death, have been reported in patients with HIV infection who were treated with hydroxyurea and other ARV drugs. Use with didanosine and stavudine have led to fatal hepatic cases, and concurrent use of hydroxyurea with these ARVs should be avoided.

Use of a live vaccine in a patient taking hydroxyurea may result in severe infections and should be avoided.

Hydroxyurea may lead to falsely elevated laboratory values for uric acid, urea, or lactic acid.

Because voxelotor (Oxbryta) is primarily metabolized by cytochrome p450 3A4 (CYP3A4), avoid use of voxelotor with strong (e.g., rifampin) or moderate (e.g., efavirenz) CYP3A4 inducers. The dose of voxelotor should be increased when co-administration with one of these agents cannot be avoided or when taken with moderate CYP3A4 inducers. To prevent increased drug exposure and an increased risk of adverse events, use of voxelotor should be avoided or its dose should also be adjusted in patients also taking a strong CYP3A4 inhibitor (e.g., ketoconazole) or fluconazole. Voxelotor may increase systemic exposure of midazolam. Use of voxelotor should be avoided in patients who take known CYP3A4 substrates with narrow therapeutic windows.

Because voxelotor could alter or interfere with measuring Hb or its subtypes, patients should not take voxelotor at the time of laboratory analysis if exact Hb measurement is required.

Drug interaction studies have not been performed with L-glutamine (Endari).

ADVERSE EFFECTS^{41,42,43,44,45}

| | Headache | Diarrhea | Abd. Pain | Nausea | Fatigue | Arthralgia | Back pain | Pyrexia |
|-----------------------------------|-----------|-----------|-----------|-----------------------|-----------|------------|-----------|-----------------------|
| crizanlizumab-tmca (Adakveo) | nr | < 10 | < 10 | 18 (11) | reported* | 18 (8) | 15 (11) | 11 (7) |
| hydroxyurea (Droxia) | reported* | reported* | nr | reported [†] | nr | nr | nr | reported [†] |
| hydroxyurea (Siklos) (pediatrics) | 7 | nr | nr | 2.5 | nr | nr | nr | 8 |
| L-glutamine (Endari) | 18 (15) | nr | 17 (16) | 19 (14) | nr | nr | 12 (5) | nr |
| voxelotor (Oxbryta) | 26 (22) | 20 (10) | 19 (13) | 17 (10) | 14 (10) | nr | nr | 12 (7) |

nr = not reported; Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive.

* Associated with infusion-related reactions

[†] Postmarketing reports

As with all therapeutic proteins, there is potential for immunogenicity with crizanlizumab-tmca (Adakveo). In a single-dose study in healthy patients (n=61), 1 patient tested positive for anti-drug antibodies (ADA). In a single-arm study in patients with SCD (n=45), ADAs were not reported in any of the patients treated with crizanlizumab-tmca. Infusion-related reactions were reported in 3% of patients treated with crizanlizumab-tmca in clinical trials.

The safety of hydroxyurea capsule (Droxia) was assessed in 299 patients with sickle cell anemia. The most common adverse reactions were hematologic-related, with neutropenia and low reticulocyte and platelet levels requiring interruption of therapy in almost all patients. Hematologic recovery typically occurred within 2 weeks. Other adverse effects reported included hair loss, macrocytosis, bleeding, and melanonychia. In addition, there have been postmarketing reports of drug-induced fever (> 102°F) requiring hospitalization that occurred with gastrointestinal, pulmonary, musculoskeletal, hepatobiliary, dermatological, or cardiovascular symptoms in patients treated with hydroxyurea capsule. Onset typically occurred within 6 weeks of starting hydroxyurea and resolved upon discontinuation of therapy. Fever reoccurred, typically within 24 hours, upon restarting therapy.

The safety of hydroxyurea tablet (Siklos) was evaluated in 405 pediatric patients ages 2 to 18 years with sickle cell disease. Infection (40%) and myelosuppression with mild to moderate neutropenia (21%) were the most frequently reported adverse effects. Patients ages 2 to 16 years had a higher risk of neutropenia than patients older than 16 years. Skin manifestations (e.g., depigmentation/melanonychia, rash, alopecia; 9%), constipation (2.5%), and vitamin D deficiency (6%) were also reported.

Other adverse effects reported more commonly with L-glutamine (Endari) than with placebo, respectively, include constipation (21% versus 18%), cough (16% versus 14%), pain in extremity (13% versus 7%), and chest pain (12% versus 8%).

Rash was reported more commonly with voxelotor (Oxbryta) treatment than in patients treated with placebo (14% versus 10%, respectively).

SPECIAL POPULATIONS^{46,47,48,49,50}

Pregnancy

Data are insufficient in humans to inform of drug-related risks to the mother or fetus with crizanlizumab-tmca (Adakveo) use during pregnancy; however, animal studies suggest a risk for fetal harm.

Data are also insufficient to inform of hydroxyurea-associated maternal and fetal risks when used during pregnancy; however, fetal harm is also expected based on findings from animal studies and hydroxyurea's mechanism of action. Pregnancy status should be confirmed in females of reproductive potential prior to starting hydroxyurea therapy. Hydroxyurea (Droxia, Siklos) may inhibit male fertility and damage spermatozoa, potentially resulting in genetic abnormalities. Female patients of reproductive potential and male patients with female sexual partners of reproductive potential should use effective contraception during treatment and for 6 or 12 months after discontinuation of treatment with Siklos and Droxia, respectively.

There are no available data regarding the use of L-glutamine (Endari) or voxelotor (Oxbryta) in pregnant women to inform of maternal or fetal risks.

Pediatrics

The safety and efficacy have not been established in patients < 5 years for L-glutamine, in patients < 12 years for voxelotor, and in patients < 16 years for crizanlizumab-tmca.

Safety and efficacy of hydroxyurea tablet (Siklos) have been demonstrated in patients 2 to 18 years of age with SCD; however, safety and efficacy of hydroxyurea capsule (Droxia) have not been established in pediatric patients.

Geriatrics

Clinical trials did not include an adequate number of patients ≥ 65 years of age to inform of differences in pharmacokinetics of crizanlizumab-tmca compared to younger patients.

The clinical trials of hydroxyurea capsule (Droxia), L-glutamine, and voxelotor did not include an adequate number patients aged ≥ 65 years to determine if they respond differently compared to younger patients.

Hepatic Impairment

The effect on the pharmacokinetics of crizanlizumab-tmca in patients with hepatic impairment is unknown. The safety of L-glutamine has not been established in patients with hepatic impairment.

Hematologic status should be monitored more frequently in patients treated with hydroxyurea who have decreased hepatic function.

The dose of voxelotor should be reduced when administered to patients with severe hepatic impairment due to increased exposure to voxelotor.

Renal Impairment

The effect on the pharmacokinetics of crizanlizumab-tmca in patients with renal impairment is unknown. The safety of L-glutamine has not been established in patients with renal impairment.

Exposure of hydroxyurea is elevated in patients with creatinine clearance (CrCl) < 60 mL/min. The hydroxyurea dose should be reduced and hematologic parameters should be monitored in these patients.

DOSAGES^{51,52,53,54,55}

| Drug | Dosage | Availability |
|------------------------------|--|--|
| crizanlizumab-tmca (Adakveo) | 5 mg/kg by IV infusion over 30 minutes given by a HCP at week 0 and week 2, followed by maintenance dosing every 4 weeks May be used as monotherapy or with hydroxyurea | Single-dose vial (SDV): 100 mg/10 mL |
| hydroxyurea (Droxia) | Initial dosage is 15 mg/kg orally once daily; if blood counts are in an acceptable range, the dose may be increased by 5 mg/kg/day every 12 weeks; Maximum daily dose of 35 mg/kg, or the highest dose that does not produce toxic blood counts, over 24 consecutive weeks | Capsules: 200 mg, 300 mg, 400 mg |
| hydroxyurea (Siklos) | Initial dosage is 20 mg/kg orally once daily; if blood counts are in an acceptable range, the dose may be increased by 5 mg/kg/day every 8 weeks or if a painful crisis occurs; Administer until mild myelosuppression (ANC of 2,000 cells/mm ³ to 4,000 cells/mm ³) is achieved; maximum daily dose of 35 mg/kg | Tablets: 100 mg, 1,000 mg Scored tablets may be split to achieve desired dose |
| L-glutamine (Endari) | Weight-based dosing: <ul style="list-style-type: none"> < 30 kg: administer 5 g orally twice daily 30 to 65 kg: administer 10 g orally twice daily > 65 kg: administer 15 g orally twice daily | Powder packets: 5 grams powder |
| voxelotor (Oxbryta™) | 1,500 mg (3 tablets) orally once daily with or without food Swallow tablet whole; do not crush, chew, or cut May be used as monotherapy or with hydroxyurea | Tablet: 500 mg |

ANC = absolute neutrophil count; HCP = healthcare provider

In patients with moderate hepatic impairment (Child-Pugh Class C), the crizanlizumab-tmca dose should be reduced to 1,000 mg once daily. In addition, a dose adjustment of crizanlizumab-tmca is required for patients taking CYP3A inhibitors or inducers. With concurrent strong CYP3A inhibitors or fluconazole, reduce the dose to 1,000 mg once daily. Concurrent use with moderate or strong CYP3A inducers requires a crizanlizumab-tmca dose of 2,500 mg once daily.

If a dose of crizanlizumab-tmca is missed, it is recommended to administer the next dose as soon as possible. If the next dose is administered within 2 weeks after the missed dose, dosing may be continued according to the patient's original schedule. If the next dose is administered more than 2 weeks after the missed dose, dosing should be every 4 weeks subsequently.

Hydroxyurea should be administered orally at the same time each day with a glass of water. Hydroxyurea tablets (Siklos) may be dispersed in a small amount of water (~5 mL) and consumed immediately for patients who cannot swallow tablets. Hydroxyurea capsules (Droxia) should be swallowed whole and not opened, broken, or chewed. Hydroxyurea is a cytotoxic drug; therefore, special handling and disposal apply.

During therapy with hydroxyurea, monitor patient's blood count every 2 weeks. Dosage increases should only be made if blood counts are in an acceptable range. Toxic ranges are defined as neutrophils $\geq 2,000$ cells/mm³, platelets $\geq 80,000$ cells/mm³, Hb > 5.3 g/dL, and reticulocytes $\geq 80,000$ cells/mm³ (if Hb < 9 g/dL). Therapy should be interrupted if blood counts reach a toxic range and may be restarted at a

reduced dose (2.5 mg/kg/day with Droxia and 5 mg/kg/day with Siklos) after hematologic recovery. A stable dose with no hematologic toxicity for 24 weeks should be achieved before increasing the dose. If hematologic toxicity recurs, permanently discontinue hydroxyurea therapy. Clinicians may use fetal hemoglobin (HbF) values to evaluate hydroxyurea efficacy which is monitored every 3 to 4 months for at least a 2-fold increase over baseline level. In patients with a CrCl < 60 mL/min or with end-stage renal disease (ESRD), reduce the hydroxyurea (Siklos) dose by half, and administer after hemodialysis in patients with ESRD.

L-glutamine powder should be mixed with 8 ounces of a cold or room temperature beverage (e.g., water, milk, apple juice) or 4 to 6 ounces of food (e.g., applesauce, yogurt) and consumed immediately. Complete dissolution of powder is not necessary.

The dosage of voxelotor in patients with severe hepatic impairment (Child Pugh C) is 1,000 mg once daily. The dosage should be reduced to 1,000 mg once daily in patients on concomitant strong CYP3A4 inhibitors or fluconazole. The daily dosage should be increased to 2,500 mg in patients also taking a strong or moderate CYP3A4 inducer.

CLINICAL TRIALS

Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all brand names in this class. Randomized, comparative, controlled trials performed in the United States comparing agents within this class in an outpatient setting for the approved indications are considered the most relevant in this category. Placebo-controlled trials are included if no head-to-head trials are available. Likewise, open-label trials were included if no comparison trials were available. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Using these criteria, numerous studies were found. Data were further excluded based on the following characteristics: formulation or drug not available in US, single-blind or single-dose study. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

crizanlizumab-tmca (Adakveo) versus placebo

SUSTAIN: The 52-week, double-blind trial evaluated the efficacy of crizanlizumab-tmca in 198 patients with SCD.^{56,57} Inclusion criteria were diagnosis of SCD, any genotype (homozygous hemoglobin S [HbSS], sickle hemoglobin C disease [HbSC], HbSβ⁰ thalassemia, HbSβ⁺ thalassemia, and others), and a history of 2 to 10 vaso-occlusive crises (VOCs) in the previous 12 months. Patients were randomized 1:1:1 to crizanlizumab-tmca 5 mg/kg (n=67), crizanlizumab-tmca 2.5 mg/kg (n=66), or placebo (n=65) administered via IV infusion at week 0 and week 2, and every 4 weeks thereafter for a treatment duration of 52 weeks. Randomization of patients was stratified by concomitant hydroxyurea use (Yes or No) and

by the number of VOCs in the previous 12 months (e.g., 2 to 4, 5 to 10). Occasional transfusions and pain medications were allowed as needed. The primary endpoint was the annual rate of VOCs leading to a healthcare visit, defined as an acute episode of pain caused by a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral opioids or parenteral non-steroidal anti-inflammatory drugs (NSAIDs). Other events considered to be VOCs were acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism (requiring a healthcare visit). In the intent-to-treat analysis, a lower median annual VOC rate was observed in patients who received crizanlizumab-tmca 5 mg/kg compared to patients who received placebo (1.63 versus 2.98, respectively; $p=0.01$). The median annual VOC rate in the 2.5 mg/kg crizanlizumab-tmca group was 2.01 ($p=0.18$). The frequency of VOCs was reduced regardless of SCD genotype and hydroxyurea use. Compared with 17% of placebo patients, 36% of patients treated with crizanlizumab-tmca 5 mg/kg, and 18% of patients treated with 2.5 mg/kg had an annual crisis rate of zero. The median time to first VOC was 4.1 months in the crizanlizumab-tmca 5mg/kg treatment group ($p=0.001$ versus placebo) and 2.2 months in the 2.5 mg/kg group ($p=0.14$ versus placebo), compared to 1.4 months in the placebo group. While the median annual rate of days hospitalized were less with crizanlizumab-tmca 5 mg/kg compared to placebo, but the difference was not significant (difference from placebo, -41.8%; $p=0.45$).

hydroxyurea (Droxia) versus placebo

A double-blind, placebo-controlled trial evaluated hydroxyurea in 299 adults with moderate to severe SCD, defined as ≥ 3 painful crises per year.⁵⁸ A painful crisis was defined as acute SCD-related pain that resulted in a visit to a medical facility, that lasted > 4 hours, and that required treatment with a parenteral analgesic (opioid or NSAID). Hydroxyurea treatment compared to placebo resulted in a significant decrease in the median annual rate of painful crises (2.5 versus 4.6, respectively; difference versus placebo, -46%; $p=0.001$), median annual rate of painful crises requiring hospitalization (1 versus 2.5, respectively; difference, -60%; $p=0.0027$), incidence of chest syndrome (56 versus 101, respectively; difference, -45%; $p=0.003$), number of patients transfused (55 versus 79, respectively; difference, -30%; $p=0.002$), and units of blood transfused (423 versus 670, respectively; difference, -37%; $p=0.003$). Increases in the median time to first and second painful crises were also seen with hydroxyurea compared to placebo (first crisis, 2.76 versus 1.35 months, respectively [$p=0.014$]; second crisis, 6.58 versus 4.13 months, respectively [$p=0.0024$]). In the hydroxyurea group, fetal hemoglobin (HbF) increased 4 to 12 weeks after starting therapy. The average HbF level was generally consistent with dose and plasma levels with a plateau seen at higher dosages. Based on demonstration of fewer VOCs in the hydroxyurea group, the trial was stopped after accrual was completed but before the scheduled 24 month follow-up time period was reached in all patients.

hydroxyurea (Siklos)

ESCORT HU: The open-label, single-arm trial assessed the efficacy of hydroxyurea in 405 pediatric ages 2 to 18 years with SCD.⁵⁹ Among the patients enrolled, 141 had not been previously treated with hydroxyurea. Median follow-up was 23 months (range, 12 to 80 months). Efficacy was assessed in patients ($n=141$) who were not previously on hydroxyurea, had ≥ 12 months of follow-up, and had data allowing for evaluations. The primary efficacy endpoint of absolute change in HbF level, at least 6 months after starting hydroxyurea compared to HbF level prior to treatment, was 5.9% (range, -2.2% to 34.7%). Median change in Hb level was 0.5 g/dL (range, -4.6 to 6.1) at 6 months and 0.7 g/dL at 12 months after starting hydroxyurea. After 12 months of hydroxyurea treatment, a decrease in the following measures were reported among 141 patients who did not receive hydroxyurea prior to enrollment and were in the

efficacy analysis: the percentage of patients with at least 1 VOC (from 69% to 42.5%), number of VOCs over 12 months (from 2 to 0), percentage of patients with an acute chest syndrome (from 24% to 6%), percentage of patients with ≥ 1 hospitalization due to SCD (from 75% to 42%), or percentage of patients requiring a blood transfusion after 12 months of treatment (from 46% to 23%).

L-glutamine (Endari) versus placebo

Efficacy of L-glutamine was evaluated in a double-blind, placebo-controlled, parallel-group study with a treatment duration of 48-weeks followed by 3 weeks of tapering.^{60,61} The study included 230 patients ages ≥ 5 years who had ≥ 2 painful crises within 12 months prior to screening. Patients were randomized to L-glutamine 0.3 g/kg (n=152) or placebo (n=78). Eligible patients stabilized on hydroxyurea for at least 3 months continued their therapy during the study. Two-thirds of patients in both groups were on concomitant hydroxyurea. The primary efficacy endpoint was the number of sickle cell crises (SCC) through week 48. An SCC was defined as emergency room or medical facility visits related to SCC pain that was then treated with a parenterally administered narcotic or ketorolac. SCC was also defined as the occurrence of acute chest syndrome (ACS), priapism, and splenic sequestration. The study demonstrated significantly fewer SCC in the L-glutamine group versus the placebo group over the 48 weeks (median SCC, 3 [range, 0 to 15] versus 4 [range, 0 to 15], respectively; p=0.0052). The study reported an improvement in median days to first SCC (84 days for the L-glutamine group versus 54 days for placebo), median cumulative days hospitalized (6.5 days for the L-glutamine group versus 11 days for placebo), and patients reporting acute chest syndrome (12 days for the L-glutamine groups versus 18 days in the placebo group). **Clinical benefit was observed regardless of hydroxyurea use.**

voxelotor (Oxbryta) versus placebo

HOPE: The randomized, double-blind trial enrolled 274 patients ages ≥ 12 years with SCD who experienced 1 to 10 VOCs in the past 12 months and had a baseline Hb level between 5.5 g/dL and 10.5 g/dL.^{62,63} VOC was defined as acute painful crisis or acute chest syndrome for which there was no explanation other than VOC. Patients could continue use of hydroxyurea if already taking stable doses for at least 3 months prior to enrollment. Patients were randomized 1:1:1 to treatment with daily doses of oral voxelotor 1,500 mg, voxelotor 900 mg, or placebo. The primary endpoint was Hb response rate compared to baseline at week 24. A response was defined as an increase of Hb of > 1 g/dL. In the intent-to-treat analysis, patients treated with voxelotor 1,500 mg had a significantly greater Hb response rate compared to placebo (51.1% versus 6.5%, respectively; p<0.001). Hb response rate in the voxelotor 900 mg group was 32.6%. In terms of improvement in Hb levels at week 24, the adjusted mean change in Hb level from baseline was 1.1 g/dL in the voxelotor 1,500 mg group (95% confidence interval [CI], 0.9 to 1.4; p<0.001), 0.6 g/dL in the voxelotor 900 mg group (95% CI, 0.3 to 0.8), and -0.1 g/dL in the placebo group (95% CI, -0.3 to 0.2). Improvements in Hb response rates were independent of hydroxyurea use. For the secondary endpoint of change in annualized rate of VOC compared to baseline, patients in the voxelotor groups did not experience a significant reduction in VOC frequency compared to placebo (number of crises per person-year: 2.77 with voxelotor 1,500 mg, 2.76 with voxelotor 900 mg, and 3.19 with placebo).

SUMMARY

Sickle cell disease (SCD) is a genetic red blood cell (RBC) disorder resulting in the production of abnormal, sickle-shaped hemoglobin S (HbS). SCD affects approximately 100,000 patients in the United States (US)

and is more common among African Americans, although it is also seen in people of Hispanic ancestry. The major clinical manifestations of SCD are related to hemolytic anemia and vaso-occlusion. Painful vaso-occlusion crises (VOCs) occur when abnormal RBCs adhere to blood vessel walls, resulting in blockage of small blood vessels, reduced oxygen flow to tissues, and organ damage.

A hematopoietic cell transplant (HCT) is the only cure for SCD, but its use is limited by associated risks and lack of matched donors. Blood transfusions are often used to treat and prevent complications of SCD, particularly in patients at risk for stroke; however, regular use of transfusions are associated with iron overload and alloimmunization. Outside of FDA-approved treatments, aggressive hydration plus analgesics are administered to manage VOC episodes.

Approved pharmacologic treatments in the US have differing mechanisms of action and include the oral antimetabolite hydroxyurea (Droxia, Siklos), the oral amino acid supplement L-glutamine (Endari), the oral HbS polymerization inhibitor voxelotor (Oxbryta), and the intravenous monoclonal antibody crizanlizumab-tmca (Adakveo). The American Society of Hematology 2020 guidelines on management of sickle cell and acute and chronic pain suggest that there is lack of comparative-effectiveness data between hydroxyurea and other disease-modifying therapies and chronic transfusions to make a recommendation on the use of these agents in treatment of acute and chronic pain, although hydroxyurea was recommended by the National Heart, Lung, and Blood Institute's (NHLBI) in 2014 guidelines to treat associated pain that interferes with daily activities.

There are no comparative trials between the agents, but clinical trials with crizanlizumab-tmca, hydroxyurea (Droxia, Siklos), and L-glutamine reported a reduction in the rate of VOCs. While voxelotor was shown to reduce hemolysis and anemia in patients with SCD in clinical trials, it did not demonstrate a statistically significant improvement in VOC occurrence. Clinical trials also demonstrated efficacy for L-glutamine, crizanlizumab-tmca, and voxelotor regardless of use with hydroxyurea.

Hydroxyurea tablet (Siklos) is indicated for use in pediatric patients ages ≥ 2 years, and hydroxyurea capsule (Droxia) is approved for use only in adults. The remaining products are approved for use in pediatrics, with L-glutamine indicated in patients ages ≥ 5 years, voxelotor in those ages ≥ 12 years, and crizanlizumab-tmca approved in patients ≥ 16 years.

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